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## REVIEW

# Pneumococcal vaccination in adults: Does it really work?

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Received 22 March 2011; accepted 13 July 2011

Available online 4 August 2011

**KEYWORDS**Pneumococcus;  
Vaccine;  
Polysaccharide;  
Conjugate;  
Efficacy**Summary**

The universal burden of pneumococcal disease is high. As pneumococcal capsular antigens induce serotype specific antibodies, both the available vaccines (polysaccharide and polysaccharide conjugated) are able to produce serological response. However, there is reasonable skepticism about the effectiveness and efficacy of the 23-valent polysaccharide vaccine, especially in the elderly and in immunocompromised adults. Results from numerous studies are conflicting but the more recent data suggest that polysaccharide vaccine raises inadequate protection against non-bacteremic pneumonia, while the benefit against invasive pneumococcal disease in high-risk population is uncertain. On the contrary, conjugate vaccine, -originally indicated only for infants and young children- appears to be highly effective but it does not cover the tremendous diversity of pneumococcal serotypes being able to cause disease in adults. Despite this, there is growing evidence that conjugate vaccines, due to their superior immunogenicity, could also be offered for adult vaccination, but still there are certain issues that warrant further investigation.

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**Abbreviations:** CAP, Community acquired pneumonia; PPV, Pneumococcal polysaccharide vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine; PCV, Pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

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## Introduction

*Streptococcus pneumoniae* (pneumococcus) is a Gram-positive diplococcus responsible for a spectrum of non-invasive (mucosal) infections such as paranasal sinusitis, otitis media and lobar pneumonia as well as invasive diseases, including meningitis, bacteremia, bacteremic pneumonia and/or empyema. It is widely accepted that *S. pneumoniae* is the most commonly identified causative organism in cases of community-acquired pneumonia (CAP) in both ambulatory and hospitalized patients worldwide.

*S. pneumoniae* is a major source of morbidity and mortality, particularly in the very young and in the elderly. In the United States, approximately 500,000 cases of pneumonia, 50,000 episodes of bacteremia and 3000 cases of bacterial meningitis are attributed to *S. pneumoniae* each year, with a case-fatality rate of 5–7%, 20% and 30% respectively.<sup>1</sup> In Europe, the incidence of CAP due to *S. pneumoniae* appears to be higher than in other continents.<sup>2</sup> Globally, pneumococcal disease is responsible for an estimated 1.6 million deaths yearly and is the leading cause of death from a vaccine-preventable disease in children younger than 5 years of age.<sup>3,4</sup> Infections caused by *S. pneumoniae* are also responsible for substantial morbidity and mortality in adults with medical comorbidities or in those older than 65 years of age, who are considered to be at increased risk for invasive pneumococcal disease.<sup>5</sup>

Pneumococci are grouped into many serotypes (~91) on the basis of their chemically and serologically distinct capsular polysaccharides. Certain serotypes are much more likely than others to be associated with clinically apparent infections, to cause severe invasive infections and to acquire resistance to one or more classes of antibacterial agents.<sup>6</sup> Proteins or enzymes on the surface of *S. pneumoniae* are important in pathogenesis of the disease because they neutralize innate and adaptive host defense mechanisms, thus enabling bacterial adhesins to promote attachment of pathogen to respiratory epithelium.<sup>7</sup> They also facilitate colonization (i.e. nasopharynx), adherence and host invasion. Progression from colonization to invasive

disease is dependent on interplay between virulence and host defense.

## Licensed pneumococcal vaccines

Due to large serotype diversity in pneumococcus, vaccines that induce antibody responses against multiple capsular antigens have had to be developed. The capsular polysaccharides of 23 serotypes (including the 6 that cause the most invasive pneumococcal infections) comprise non-conjugated pneumococcal polysaccharide vaccine (PPV), which was licensed for adults in 1983. The vaccine covers 85–90% of serotypes responsible for invasive disease.<sup>1</sup> There are two 23-valent pneumococcal vaccines (PPV23): one that is used in the United States, Europe, and elsewhere (Pneumovax<sup>®</sup> 23) and another that is used in Europe and Canada (Pneumo<sup>®</sup> 23). The 0.5 ml dose of the vaccine contains 25 µg of polysaccharide for each of the 23 included serotypes in isotonic saline solution with 0.25% phenol as a preservative. Pneumococcal capsular polysaccharide are highly antigenic and therefore are able to induce serotype-specific antibodies that enhance opsonization, phagocytosis and killing by host immune response.<sup>8</sup> A twofold or greater increase in serotype-specific antibody develops within three weeks in 80% or more of healthy young adults.<sup>1</sup> Non-conjugated pneumococcal polysaccharide vaccines activate B-cells but elicit T-cell independent immune responses. As a result, they do not elicit protective immune responses in children aged less than approximately 2 years, they do not induce immune memory and they devoid of booster effect. In addition, polysaccharide vaccines do not induce mucosal immunity and thus they have little or no impact on nasopharyngeal carriage.<sup>9–11</sup>

Polysaccharide vaccines are widely recommended for use in adults who are at the highest risk of invasive pneumococcal disease including individuals with a history of chronic lung disease, heart failure, chronic renal failure (including nephrotic syndrome), chronic liver disease (including alcohol dependence and cirrhosis), diabetes mellitus, asplenia/sickle cell disease, immunocompromised individuals, such as those with HIV/AIDS or blood borne

dyscrasias, patients with cochlear implants or chronic cerebrospinal fluid leak, residents of nursing homes and other long-term care facilities and all individuals older than 65 years. PPV23 is now also recommended for all asthmatics 18 years and older, and all individuals who smoke, irrespective of whether or not they have any coexisting risk factors<sup>12</sup> (Table 1).

Pneumococcal conjugate vaccines (PCVs), in which each of the selected bacterial capsular polysaccharides is coupled with a protein carrier molecule, have been a major advance in the prevention of invasive pneumococcal disease.<sup>13</sup> The 7-valent PCV (PCV7, Prevnar®/Prevenar®) employs an inactivated diphtheria CRM197 toxoid as the carrier protein for all seven serotypes which helps improve its immunogenicity. This vaccine was first licensed in the USA in 2000 and subsequently has become available in approximately 90 countries worldwide. In contrast to the 23-valent non-conjugated vaccine, the conjugated vaccines activate B- and T-cell leading to immune memory. They elicit strong adaptive and booster response. As a result, they are immunogenic in infants under two years of age. In addition, PCV 7 elicits mucosal immune responses in immunized hosts most probably due to induction of IgA antibodies. Mucosal immunity enables asymptomatic carriers to eradicate colonizing pneumococci of vaccine serotypes.<sup>14</sup> Since 2006, PCV is recommended in routine immunization schedules for children of this age, with prioritization of their introduction in countries with high child mortality rates and/or high rates of HIV infection.<sup>15</sup>

Pneumococcal conjugate vaccines that contain three (PCV10, Synflorix®) or six serotypes (PCV13, Prevnar 13®/Prevenar 13®) in addition to those in the 7-valent PCV have recently become available for use in infants and young children in some countries.<sup>16</sup>

## 23-Valent polysaccharide vaccine

The safety of PPV23 is well documented. Local reactions, usually mild and self limited, occur in 30%–50% of the patients. Fever or myalgias occur in about 1% of the patients. Serious adverse events are rare.<sup>17</sup> There is about a 3-fold increase in local reactions with revaccination, but no increase in systemic or serious reactions is noted.<sup>17,18</sup> Even though the vaccine is safe, immunization rates remain low, ranging from 12.6% to 36.5% for at risk people in

Europe.<sup>19</sup> A wide range of factors, including demographic, comorbidity, quality of life, social support and lifestyle have been associated with pneumococcal vaccination status among older adults with clinically diagnosed CAP.<sup>20</sup>

PPV may provide suboptimal protection of older adults because antibody responses or even functional activity, as measured by the elicitation of opsonophagocytic antibodies after vaccination may be found lower in elderly for a number of evaluated serotypes.<sup>21–23</sup> It is suggested that non-response to specific serotypes is the likely cause for vaccination failure in the elderly; hence 23-valent pneumococcal vaccine should be regarded as 23 different vaccines.<sup>24</sup> Furthermore, immune responses are typically lower and less robust in individuals with co-morbidities including cirrhosis, chronic obstructive pulmonary disease, diabetes mellitus or immune-mediated inflammatory diseases.<sup>1,25,26</sup> In the population of COPD patients, clinical and laboratory studies have suggested that the currently approved vaccine is less effective than in healthier patients and to date no randomized-controlled trial of pneumococcal vaccination for COPD patients has demonstrated any beneficial effect.<sup>25</sup> Nevertheless, the administration of systemic steroids does not influence the antibodies response in these patients.<sup>27</sup> Immunocompromised patients, such as human immunodeficiency virus (HIV)-infected persons, alcoholics and diabetics are less likely to respond to vaccination with pneumococcal polysaccharides; in these patients antibody responses may be markedly diminished or even absent.<sup>28,29</sup>

## Revaccination- duration of immunity

Vaccination with PPV23 produces a peak rise of the levels of antibodies which thereafter progressively fall, during the following 5 to 10 years. This fall is more prominent in some populations. However, it should be underlined that it is not known what level of antibody is protective. Current recommendations for revaccination support 1-time revaccination after 5 years in persons with functional or anatomic asplenia, in immunocompromised conditions and also in individuals older than 65 who were first immunized before the age of 65<sup>12</sup> (Table 2). Multiple revaccinations are not recommended because of insufficient data regarding clinical benefit, particularly the degree and duration of protection and safety.<sup>12</sup> Actually, the benefit of revaccination remains uncertain since vaccination with pneumococcal polysaccharide antigens may induce hyporesponsiveness on rechallenge. Antibody response occurs after a second dose, but it is less robust after the second compared with the first dose.<sup>30,31</sup> Thus, although revaccination leads to an immunological response, administration of a first dose of vaccine may blunt the immune response to subsequent doses.<sup>32</sup> This may potentially be associated with a corresponding decrease in the magnitude of clinical protection provided by revaccination. These observations were challenged by a recent publication which concluded that repeat revaccination with PPV was immunogenic to Alaskan adults aged 55–74 years.<sup>33</sup> Notably, there is some evidence that 7-valent pneumococcal conjugate revaccination of seniors previously vaccinated with PPV23 provides a stronger immune response.<sup>34</sup>

**Table 1** PPV23 Vaccination: Summary of indications.<sup>12</sup>

### Persons at risk for pneumococcal infection

Individuals older than 65 years
History of chronic disease
Immunocompromised individuals (HIV/AIDS or blood borne dyscrasias)
Patients with cochlear implants or chronic cerebrospinal fluid leak
Residents of nursing homes and other long-term care facilities
Asthmatics 18 years and older
Smokers

**Table 2** PPV23 Revaccination: Summary of indications.<sup>12</sup>

Revaccination: 1-time revaccination after 5 years

Persons with functional or anatomic asplenia  
 Immunocompromised persons  
 Individuals older than 65 if vaccinated  $\geq$  5 years  
 previously when  $<$  65 years old

## Effectiveness against invasive disease

Although the PPV has been widely introduced into vaccination programs for elderly people and high-risk populations, the degree of protection afforded remains a controversial issue. A number of case-control and cohort studies provide support for the effectiveness of PPV23 in reducing the risk of invasive disease in immunocompetent older adults.<sup>29,35–42</sup> In the largest case-control study of PPV23 effectiveness, a total of 983 cases of invasive pneumococcal disease were evaluated; the study identified an efficacy of 47% for all patients and 53% for immunocompetent adults regardless of the serotype causing the illness, but only 21% for the immunocompromised patients when they were infected by a strain represented in the vaccine.<sup>35</sup> These results support the use of pneumococcal polysaccharide vaccine to prevent bacteremic disease in adults aged 65 years or over.<sup>43</sup> Nevertheless, a decrease in vaccine effectiveness both with age and with time since vaccination was demonstrated in the aforementioned study.<sup>35</sup> Finally, the protective value of polysaccharide vaccine in invasive pneumococcal disease was recently reviewed by a synthesis of 9 different meta-analyses, showing substantial efficacy in all adult population (83%–63%) but not in high-risk population (0%–42%) for all serotypes.<sup>44</sup> The same review concluded that the effect of the PPV23 on mortality prevention from either invasive disease or pneumonia, was very limited, if any.

## Efficacy against non-bacteremic pneumococcal pneumonia

Both influenza vaccine and PPV have been reported as protective factors against CAP.<sup>45,46</sup> However, the protective effect of PPV against pneumococcal pneumonia without bacteremia is unclear.

In a prospective randomized study which included 1006 nursing home residents in Japan, PPV23 prevented pneumococcal pneumonia and reduced mortality from pneumonia among nursing home residents the majority of whom are very old and have co-morbidities.<sup>47</sup> Also in hospitalized patients with CAP, prior vaccination against pneumococcus was associated with improved survival, decreased chance of respiratory failure or other complications, and decreased length of stay.<sup>48</sup> Similarly, a Canadian 6-hospital-based prospective observational study concluded that although PPV23 possibly fails to prevent CAP, it could modify the severity of the infection lowering mortality (as much as 40%) or ICU admission, thus suggesting the persistence of the current adult pneumococcal vaccination guidelines.<sup>49</sup>

On the contrary, an early randomized, double-blind, placebo-controlled trial testing the efficacy of the 14-valent PPV in 2295 high-risk patients failed to prove protection against pneumonia or bronchitis.<sup>50</sup> Furthermore, in a retrospective study of a large population of 47,365 older adults, pneumococcal vaccination was associated with a significant reduction in the risk of pneumococcal bacteremia but did not alter the risk of outpatient pneumonia or of any case of community-acquired pneumonia.<sup>51</sup> These results are consistent with those of four meta-analyses of prospective randomized trials of PPVs, all of which concluded that there is no evidence that the vaccine is associated with a reduction in the risk of pneumonia from any cause among older adults.<sup>52–55</sup>

According to a meta-analysis by Melegaro et al, PPV23 vaccine efficacy against invasive pneumococcal disease in the general elderly population is 65% (95% CI: 0.49–0.92) whereas it has a moderate effect in the high-risk elderly with an efficacy of 20% (95% CI: 1.88–0.78). The vaccine has little or no effects against pneumonia in the general elderly (efficacy 16%) while in high-risk elderly individuals it is only about 20% efficacious.<sup>56</sup> Similarly, in a recent meta-analysis which included 22 trials involving 101,507 participants, there is little evidence of vaccine protection among elderly patients or adults with chronic illness for presumptive pneumococcal pneumonia (RR 1.04, 95% CI 0.78–1.38), for all-cause pneumonia (RR 0.89, 95% CI 0.69–1.14) and for all-cause mortality also (RR 1.00, 95% CI 0.87–1.14).<sup>57</sup>

## Cost-effectiveness

Despite the skepticism about the actual efficacy of the PPV23, an analysis of the published literature identified 11 economic evaluations, all supporting the cost-effectiveness of PPV23.<sup>58</sup> However, most of these studies were conducted before the introduction of 7-valent PCV into infant immunization schedules. Since it is shown that age groups not targeted to receive PCV7 have reduced rates of invasive disease as a result of indirect protection (see text below), this issue may warrant re-analysis.<sup>3</sup> Moreover, the outcomes of these studies depend on a variety of factors, such as the characteristics of the populations, the end-points, invasive pneumococcal disease incidence, case-fatality and the applied vaccine efficacy. For example, European and American studies supporting cost-effectiveness of PPV23 accept the assumption that the effectiveness of the vaccine for persons  $>$ 65 years ranges from 75% in the 1st year to 33% in the 6th year, a fact that is highly debatable.<sup>59,60</sup>

## Polysaccharide conjugate vaccines

### Clinical efficacy of pneumococcal conjugate vaccines

PCVs have been an important landmark in the global control of pneumococcal disease. The routine use of the 7-valent PCV has resulted not only in tremendous reduction of invasive infection in children but also in decrease in rates of pneumococcal disease in the elderly population, thus



indicating that there is an indirect beneficial effect on unvaccinated persons.<sup>61,62</sup> Unlike the PPV23, the pneumococcal conjugate vaccine is effective in reducing nasopharyngeal carriage of serotypes included in the vaccine and some types that are not included. Obviously, a diminution of the carrier rate reduces the transmission to non-carriers and the risk of subsequent disease. Because of this, the vaccine induces what is referred to as "herd immunity," i.e. immunizing a proportion of the population in any community reduces disease in unvaccinated individuals.<sup>63</sup>

Correspondingly, use of the PCV7 has led not only in a rapid fall in pneumococcal disease rates among children but also to a major decline in the prevalence of invasive pneumococcal disease and a modest decrease in respiratory tract infections in adult population.<sup>64</sup> On the other hand, rates of invasive disease due to some non-PCV serotypes have somewhat increased, including rates of disease due to serotypes included in PPV (especially 19A)<sup>65</sup> and serotypes not present in either vaccine (such as 23A). As a result, in the United States during the era of widespread PCV7 vaccination, the annual incidence of disease among children and elderly due to non-vaccine serotypes is increasing.<sup>66</sup> This is a point of particular concern because an everlasting emerge of replacement strains renders the formulation of conjugate vaccines a moving target.<sup>67</sup> In addition, a serotype-specific immune unresponsiveness to PCV following invasive pneumococcal disease has been observed.<sup>68</sup>

Interestingly, the introduction of the pediatric conjugate vaccine was associated with an overall decrease in invasive disease among HIV-infected adults, despite increased disease caused by non-vaccine serotypes.<sup>69</sup> Moreover, it has been shown that a 9-valent PCV was quite effective in preventing pneumonias associated with respiratory viruses, providing evidence that pneumococcus has a major role in the development of such pneumonias and that viruses contribute to the pathogenesis of bacterial pneumonia.<sup>70</sup>

## Experience in adults

The remarkable success of protein-conjugate vaccines among young children has renewed interest in the possible use of these vaccines in older adults. Possible advantages of PCVs in elderly adults may include higher levels of protection against the vaccine serotypes after vaccination and the ability to prolong the duration of protection by use of repeated vaccinations over time.<sup>71</sup> Preliminary studies in healthy adults older than age 70 years have shown that PCV7 induces greater functional antibody activity at one month post vaccination than does PPV23, although this response is reduced in those who have been previously vaccinated.<sup>72,34</sup> In this population the 1.0-ml dose of PCV7 induced a greater immune response than the pediatric 0.5-ml dose (containing 2 µg of capsular polysaccharide from serotypes 4, 9 V, 14, 18C, 19F, and 23F and 4 µg of serotype 6B). No additional benefit was observed with a 2.0-ml dose.<sup>34</sup> In patients with COPD, PCV7, when given at twice the dose recommended for children, induced a superior immune response at one month post vaccination compared with PPV23. In the same study, both older age and prior

PPV23 vaccination were shown to impair PCV7 responsiveness.<sup>73</sup> Taken together, these studies suggest that although protein-conjugate vaccines may induce superior immune responses compared to the polysaccharide vaccine, the optimal dose in adults is uncertain and higher doses may be needed in those previously vaccinated with PPV23. Furthermore, despite the greater immunogenicity of PCV7, it is not clear that the vaccine will prevent acute exacerbations of COPD.<sup>73</sup>

Another important limitation of PCVs is the low serotype coverage. The 13-valent PCV (PCV13), which offers greater serotype coverage than PCV7, is currently being evaluated in clinical trials in healthy adults.<sup>74,75</sup> CAPITA (Community Acquired Pneumonia Immunization Trial in Adults) is a randomized, placebo-controlled trial, with a 1:1 random allocation planned to establish the efficacy of the 13-valent PCV vaccine in the prevention of a first episode of vaccine serotype specific pneumococcal pneumonia in 85,000 community-dwelling adult persons aged 65 years and older.<sup>76</sup> The study will take place in the Netherlands where a large group of adults  $\geq 65$  years, naive to PPV23, is available which makes it possible to conduct a large placebo-controlled efficacy study in this age group.

Finally, as there is accumulating evidence that incidence of pneumococcal disease in adults in the United States and Europe is decreasing and given that cost of PCV13 is substantially higher than PPV23, the cost-effectiveness of possible PCV widespread adult vaccination is questionable. Besides, higher cost could be prohibitive for developing countries.<sup>67</sup> On the other hand, the favorable outcome of PCV vaccination in HIV-infected adults in Africa, shown in a recent randomized clinical efficacy trial, supports PCV as an additional intervention for improving care in that patient population.<sup>77</sup>

## Conclusions

As pneumococcal infections cause a large burden of disease worldwide, the control of this disease with an efficacious vaccine is highly desirable. Effective prevention of pneumococcal CAP and invasive pneumococcal disease through influenza or pneumococcal vaccination has been a high-priority issue for health policy makers worldwide. An overall assessment of the published studies possibly derives the following conclusions:

- PPV vaccination appears cost effective for the elderly although the vaccine might only be effective in preventing invasive disease.
- Due to limited immunogenicity in those with underlying high-risk conditions, PPV23 provides incomplete protection, especially in the immunocompromised and elderly patients.
- PPV does not appear to be particularly effective in preventing pneumonia, even in populations for whom the vaccine is currently recommended. It is also uncertain whether PPV could have any modifying effect on the severity of the disease or the mortality rate. These underscore the critical need to evaluate other vaccine formulations for the prevention of non-invasive pneumococcal infections in adults and require the

development of more effective pneumococcal vaccination strategies.<sup>78</sup>

- The introduction of PCV as a routine vaccination for infants not only reduced invasive infection in children but had an indirect protective effect on unvaccinated persons. Newer formulation of PCV including additional 13 serotypes could prove to be good future option. However, its use in adult population needs to be thoroughly evaluated.
- The phenomenon of serotype replacement in which decreases in disease due to vaccine-type *S. pneumoniae* are counterbalanced by increases in disease due to non-vaccine serotypes, may ultimately limit the protection offered by any serotype-specific vaccine.<sup>71</sup>

New options for future vaccine development include a number of protein-based pneumococcal vaccine candidates which offer the potential advantage of serotype-independent protection as well as the increasing availability of adjuvants.<sup>78,79</sup>

## Conflict of interest statement

There are no financial (such as employment, consultancy, stock ownership, honoraria and paid expert testimony) or other forms of conflict of interest (including personal, academic and intellectual issues) for any of the authors.

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